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Severity and outcomes of community acquired pneumonia in asthmatic patients

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Summary
Background: Limited information is available about clinical outcomes and microbiology of community-acquired pneumonia in asthma.
Methods: We prospectively studied 4079 CAP patients over a 12-years period and found 139 (3.4%) asthmatic patients.
Results: Asthmatics showed younger age (57 ± 19 vs. 66 ± 19 years), less males (32% vs. 68%) and less active smokers (15% vs. 25%). Moreover, they had used more frequently inhaled corticosteroids (ICs, 53% vs. 17%, $p < 0.001$) and antibiotics (32% vs. 24%, $p = 0.041$). In

Abbreviations list: CAP, community-acquired pneumonia; ICs, inhaled corticosteroids; IPD, invasive pneumococcal disease; PSI, pneumonia severity index; CURB-65, confusion, blood-urea nitrogen, respiratory rate, blood pressure, age; TBAS, tracheobronchial aspirates; BAL, bronchoalveolar lavage; LOS, length of hospital stay; ICU, intensive care unit; PaO_2, arterial oxygen tension; F_IO_2, inspiratory oxygen; SD, standard deviation; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; % predicted, % of predicted value; SABA, short-acting β;2 agonists; LABA, long-acting β;2 agonists;"Severe CAP" presence of at least one major criterion or three minor criteria of the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines; MV, mechanical ventilation; CDC, centre for disease control; COPD, chronic obstructive pulmonary disease.

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comparison with non asthma-CAP, asthmatics showed at admission more pleuritic pain and dyspnoea but less severe pneumonia (PSI, CURB-65, PaO_2/F_IO_2 ratio; $p < 0.05$). No differences were observed in CAP microbiology, being *Streptococcus pneumoniae* the most frequent isolate. Clinical outcomes in asthmatic patients were similar to the general population (mortality, mechanical ventilation, etc.) but with a shorter median length of stay (6 [3; 9] vs. 7 [4; 10] days, $p = 0.023$). The chronic use of ICs did not influence clinical presentation and outcomes among asthmatic patients.

Conclusions: Asthmatics were younger and showed similar clinical presentation. Consistently with PSI, asthmatics showed similar outcomes than the general population. The microbial aetiology of CAP in asthma did not differ from the general population and antibiotic therapy should follow current guidelines.

Introduction

Asthma is the most common chronic airway inflammatory disease affecting children and adults with an estimated 300 million involved individuals worldwide [1,2]. In Europe asthma has a prevalence varying from 2 to >10% and is still associated with a relevant sanitary and economic burden despite improved therapeutic options.

The majority of asthmatic patients suffer mild to moderate disease that can be well controlled with standard therapy [3] allowing clinical stability. However, 5—10% of asthmatics suffer from a severe disease characterized by frequent exacerbations and poor clinical control being often refractory to usual treatment [4,5]. The principal causes of asthma exacerbations are considered the viral infections [6—8] possibly accounting for 80% of exacerbations in children and 50% in adults [9] (respiratory syncitial virus in infancy [10] and rhinovirus in adults [11]). On the other hand, bacterial infection is usually thought to play a less significant role in asthma exacerbations [8,12]. Nevertheless, two different studies described that asthmatic patients also have an increased susceptibility to bacterial infections and particularly to invasive pneumococcal disease, usually presenting as a pneumonia [13—15], (IPD). In addition, it has been described that asthma could be associated with an abnormal innate and/or acquired immune response to pneumococci [16,17], which makes the reported association between asthma and increased IPD biologically plausible [13,14]. Conversely, Lee et al. described that asthmatics have the same risk of pneumococcal pneumonia as healthy controls [18].

Nonetheless, to date the information available about epidemiology, clinical presentation and outcomes of CAP in asthma is poor and no specific recommendations are provided for these patients in current guidelines [19].

The aim of our study is therefore to determine prevalence, clinic characteristics, microbial aetiology and outcomes of asthmatic patients hospitalized for a CAP and to assess whether asthmatic patients with CAP do present different severity and/or microbiological characteristics and whether current CAP guidelines are fully applicable to this population or any particular recommendations are needed.

Methods

Patients and definitions

We prospectively studied 4079 consecutive adult patients hospitalized with CAP between January 2000 and December 2011 in two tertiary care university Hospitals in Barcelona and Valencia, Spain.

Pneumonia was defined as the presence of a new infiltrate on the chest radiograph along with signs and symptoms suggestive of a lower respiratory tract infection and no alternative diagnosis during follow-up.

Asthma was defined as the presence of the following criteria:

- Asthma diagnosis made by a specialist in respiratory or internal medicine in the medical record
- Characteristics signs and symptoms of asthma in the patient' medical history
- Chronic pharmacological treatment specific of asthma
- Spirometric data compatible with the diagnosis of asthma when available: a variable and generally reversible airflow obstruction at spirometry (when available) in accordance with current guidelines for asthma management (www.ginasthma.org update 2012).

In case the patient did not meet these criteria, he/she was excluded from the analysis in order to ensure the strictest selection of asthma patients. This multifactorial definition was used considering the potential difficulties to define asthma patients in a prospective database designed to describe all CAP patients visited in the Hospital and not specifically asthmatics.

Patients with clinical suspicion of COPD or chronic bronchitis were also excluded from the asthma group. All cases of asthma were revised by a second physician expert in asthma, external to data collection and analysis.

Exclusion criteria from our CAP database included the following: a) severe immunosuppression, such as in solid-organ or bone-marrow transplantation or AIDS, or receiving chemotherapy or other immunosuppressive drugs (>20 mg prednisone-equivalent per day for ≥2 weeks); b) hospitalization in the preceding 21 days; c) active tuberculosis; d)

cases with confirmed alternative diagnosis at the end of follow-up.

Data collection

The following data were recorded on admission to hospital: age, gender, current smoking, nursing home residency, comorbid illnesses (respiratory, cardiac, hepatic, renal, neurological, etc.), and antimicrobial treatment prior to hospital admission, duration of symptoms prior to visit, clinical symptoms, physical examination, chest X-rays pattern, blood analysis and antimicrobial treatment at admission. PSI and CURB-65 score classes (Online Supplemental Material), the need of mechanical ventilation (invasive and non-invasive) and ICU, the development of systemic (septic shock, bacteraemia, acute renal failure, diarrhoea, etc) or pulmonary (multilobar infiltration, atelectasis, pleural effusion, empyema, respiratory distress) complications were recorded. "Severe CAP" was defined when at least one major criterion or three minor criteria of the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines were present [19]. Follow-up variables were length of hospital stay (LOS) and 30-day mortality. All surviving patients were re-examined or at least contacted by telephone at 30–40 days after discharge. Antibiotic therapy and its adequacy to current Spanish guidelines for CAP treatment [20] were recorded.

Asthma data included asthma treatment: short acting β-agonists (SABA), long acting β-agonists (LABA), inhaled and systemic corticosteroids. The most recent lung function tests before pneumonia were recorded to describe functional status of asthmatic patients.

Due to the observational nature of the study, in the context of routine clinical and epidemiologic follow-up of CAP, patients' written consent was not considered necessary. Hospitals' Ethical Committees had approved routine data collection for local CAP cases for epidemiological reasons and their use for research purposes.

Microbiological evaluation

Routine sampling to determine the microbial aetiology of pneumonia included sputum, urine for *Streptococcus pneumoniae* and *Legionella pneumophila* antigens, blood cultures, nasopharyngeal swabs for respiratory viruses. Pleural puncture, tracheobronchial aspirates (TBAS) and bronchoalveolar lavage (BAL), when available were collected for Gram and Ziehl–Neelsen stains and for cultures for bacterial, fungal and mycobacterial pathogens. We only considered valid sputum samples according to current microbiological standards [21]. Serology tests for atypical pathogens were performed at admission and after 4–6 weeks (Online Supplemental Material).

Statistical analysis

We show *n* (%) for categorical variables and median (1st quartile; 3rd quartile) for continuous variables with non-normal distribution or mean (SD) for those with normal distribution. Categorical variables were compared using the Chi-square test or Fisher's exact test. Continuous variables were compared using the Student's *t*-test or the nonparametric Mann–Whitney *U* test. Univariate and multivariate logistic regression analyses were performed to identify variables predictive of patients with prolonged length of hospital stay (LOS $\geq$6 days) (dependent variable); we also performed a subgroup analysis for patients with asthma. Also univariate and multivariate logistic regression analyses were performed to predict 30-day hospital mortality (dependent variable). Variables that showed a significant result univariately ($p < 0.1$) were included in the corresponding multivariate logistic regression backward stepwise model (Online Supplemental Material). Variables highly correlated were excluded from multivariate analyses. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the models [22]. The level of significance was set at 0.05 (two-tailed). All analyses were performed with IBM SPSS Statistics 18.0 (Armonk, New York, USA).

Results

Clinical characteristics

We identified 4079 patients hospitalized with CAP from January 2000 to December 2011 with a mean ± SD age of 64 ± 19 yrs (62% of males). The most frequent comorbidities were chronic respiratory diseases ($n = 1519$ [37%], of whom COPD: 667 [17%]), chronic heart diseases (*n*: 733, 18%), neurological diseases (*n*: 653, 18%) and diabetes mellitus ($n = 657$, 17%). Furthermore, among chronic respiratory diseases, asthma was diagnosed in 139 patients (3.4% of total population). Spirometric data were available in 64 patients (46%), being the mean $FEV_1$72 ± 24[SD]% of predicted value at manoeuvres before bronchodilator.

Detailed information on asthma treatment was available in 116 patients (83%): 18 (15%) patients had no inhaled treatment at time of pneumonia; 26 (22%) were treated only with SABA on demand; 36 (30%) with a combination therapy (inhaled corticosteroids and LABA); 36 (30%) only with inhaled steroids; 6 (5%) asthmatic patients had received frequent cycles of oral steroids.

Baseline characteristics

Main patients' characteristics at admission are shown in Table 1 according to asthma presence. Asthmatics were more likely to be women, younger and less frequently current smokers. In addition, they had received more antibiotic therapy in previous 2 months prior to hospitalization and ICs treatment but no differences were observed regarding previous treatment with oral steroids.

Pneumonia severity at admission was lower for the asthma-CAP group that showed a lower PSI (Table 2), less "severe CAP" [19] cases (asthma-CAP: $n = 19$ [15%] vs. CAP: $n = 756$, [23%]; $p = 0.043$) and less hypoxaemia in comparison with the CAP group.

By contrast, asthmatic patients showed at admission a trend to more expectoration and dyspnoea and had significantly more pleuritic pain (Table 2). The laboratory data showed significantly higher leucocytosis but lower creatinine levels among asthmatic patients (Table 2).

Table 1 Baseline characteristics of study population according to the diagnosis of asthma.

Variable	Asthma-CAP *n*, (%) 139, (3.4%)	CAP *n*, (%) 3940, (96.6)	*P* value
Demographics			
Age (years), mean ± SD	57 ± 19	66 ± 19	**<0.001**
Sex, male/female, *n*	44/95	2488/1452	**<0.001**
Smoking, *n* (%)			**<0.001**
No smoker	97 (70)	1682 (43)	**<0.001**
Current smoking habit	21 (15)	971 (25)	**0.010**
Former smoking habit	20 (15)	1257 (32)	**<0.001**
Alcohol, *n* (%)			0.058
No alcohol abuse	120 (86)	3195 (82)	0.23
Current alcohol abuse	19 (14)	529 (14)	0.99
Former alcohol abuse	0 (0)	152 (4)	**0.017**
Spirometric data, mean ± SD[a]			
FEV_1/FVC (%)	67 ± 14	–	–
FEV_1 (ml)	1.91 ± 0.93	–	–
FEV_1 (% pred.)	72 ± 24	–	–
FVC (ml)	2.8 ± 1.2	–	–
FVC (% pred.)	84 ± 20	–	–
Previous ICs therapy, *n* (%)	72 (53)	643 (17)	**<0.001**
Previous oral steroid therapy, *n* (%)[b]	1 (1)	71 (2)	0.33
Previous antibiotic therapy, *n* (%)[b]	43 (32)	907 (24)	**0.041**
Previous pneumococcal vaccine, *n* (%)	11 (10)	459 (16)	0.10
Previous influenza vaccine, *n* (%)	45 (41)	1255 (43)	0.64
Nursing home, *n* (%)	0 (0)	91 (3)	0.070
Co-morbidities, *n* (%)			
Diabetes mellitus	16 (12)	641 (17)	0.11
Chronic renal failure	4 (3)	245 (6)	0.10
Chronic heart disorders	17 (12)	716 (18)	0.069
Chronic liver disease	5 (4)	169 (4)	0.68
Neurological disease	13 (10)	640 (18)	**0.026**

P values less than 0.05 are reported in bold and indicate statistically significant difference. Percentages calculated on non-missing data. Abbreviations. SD: standard deviation; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; % pred.: % of predicted value; ICs: inhaled corticosteroid.

[a] Evaluated at the last clinical control.

[b] Drugs assumed in last month; for oral steroid use only patients taking less than 20 mg of 20 mg prednisone-equivalent per day were included in the CAP database.

Microbiological aetiology

Microbiological diagnosis was achieved in 1704 (42%) patients, 69 asthmatics and 1635 non asthmatics, indicating a trend to a higher rate of microbiological diagnosis in the asthma-CAP group (asthma-CAP: 50% vs. CAP: 41%; $p = 0.056$). Distribution of the pathogens did not differ between groups being *S. pneumoniae* the most frequent isolate, followed by respiratory virus and atypical bacteria in both groups (Table 3).

Overall viral infections, including both monomicrobial and mixed infections, were found in 18 asthmatics (26%) and 311 non asthmatic (19%) patients ($p = 0.15$). The rate of bacteraemia did not differ between the 2 groups (10% vs. 8%; $p = 0.42$) and were mostly caused by *S. pneumoniae* in both groups (Table 4).

Antibiotic treatment

The most frequent initial antimicrobial treatment was a combination therapy (mostly a betalactam *plus* macrolide or quinolone) in both groups (asthma-CAP: $n = 76$ [55%]; CAP: $n = 2617$ [67%]). Within the cases of monotherapy, fluoroquinolones were the most frequent antibiotics, particularly among asthmatic patients (asthma-CAP: $n = 57$ (41%) vs. CAP: $n = 983$ (25%); $p < 0.001$). The treatment adequacy according to current Spanish guidelines for CAP treatment [20] was 96% in asthmatic patient and 92% in non asthmatic patients ($p = 0.37$).

Pulmonary and systemic complications

Both pulmonary and systemic complications of CAP are shown in Table 5. No differences were observed in the prevalence of CAP complications between asthma-CAP and CAP groups with the only exception of acute renal failure, less frequent among asthmatics (asthma-CAP: $n = 16$ (11%) vs. CAP: $n = 887$ (23%); $p = 0.001$).

Main clinical outcomes

Asthmatic patients showed similar rates of 30-day mortality (4% vs. 7%) and MV (both invasive and non invasive) and a

Table 2 Data of clinical presentation and severity assessment of study population according to asthma presence.

	Asthma-CAP *n*, (%) 139, (3.4%)	CAP *n*, (%) 3940, (96.6)	*P* value
Physical data at presentation, *n* (%)			
Cough	112 (81)	3083 (79)	0.62
Sputum	87 (64)	2189 (58)	0.11
Sputum purulence	57 (42)	1428 (38)	0.27
Dyspnoea	101 (73)	2537 (66)	0.063
Pleuritic pain	86 (63)	1572 (41)	**<0.001**
Fever	109 (82)	3119 (83)	0.82
Lower level of consciousness	16 (11)	691 (18)	0.061
Vital signs			
Respiratory rate, median (1st quartile; 3rd quartile)	24 (20; 28)	24 (20; 30)	0.079
Temperature (°C), median (1st quartile; 3rd quartile)	37.4 (36.3; 38.2)	37.6 (36.6; 38.3)	0.15
Temperature <36 °C, *n* (%)	12 (10)	191 (6)	**0.043**
Systolic blood pressure at presentation (mmHg), median (1st quartile; 3rd quartile)	123 (110; 143)	130 (115; 150)	**0.028**
Systolic blood pressure <90 mmHg, *n* (%)	9 (7)	142 (4)	0.073
Laboratory findings			
Creatinine (mg/dL), median (1st quartile; 3rd quartile)	0.9 (0.8; 1.2)	1.0 (0.8; 1.4)	**<0.001**
Creatinine ≥1.5 mg/dL, *n* (%)	13 (9)	812 (21)	**0.001**
C-reactive protein level (mg/dL), median (1st quartile; 3rd quartile)	15.1 (7.5; 28.8)	17.4 (8.7; 26.8)	0.48
C-reactive protein level ≥17 mg/dL, *n* (%)	51 (44)	1651 (51)	0.14
WBC count (x10^9 cell/L), median (1st quartile; 3rd quartile)	13900 (10800; 18400)	12400 (9000; 17100)	**0.002**
Platelets count (x10^9 cell/L), median (1st quartile; 3rd quartile)	253 (200; 305.5)	235 (181; 304)	0.054
$SatO_2$ (%),median (1st quartile; 3rd quartile)	94.8 (92.2; 96)	93.5 (90; 95.9)	**0.001**
PaO_2/F_IO_2, median (1st quartile; 3rd quartile)	304.8 (266.7; 341.7)	282.6 (242.9; 329)	**0.007**
PSI score classes I—III, *n* (%)	93 (74)	1766 (50)	**<0.001**
PSI score classes IV—V, *n* (%)	32 (26)	1800 (50)	
CURB-65 < 3, *n* (%)	86 (89)	2269 (80)	**0.042**
CURB-65 ≥ 3, *n* (%)	11 (11)	554 (20)	
Severe CAP	19 (15)	756 (23)	**0.043**
Site of care, *n* (%)			0.084
Outpatients	26 (19)	551 (14)	0.12
Ward	87 (62)	2807 (71)	**0.027**
ICU admission	26 (19)	580 (15)	0.20

P values less than 0.05 are reported in bold and indicate statistically significant difference. Percentages calculated on non-missing data. Abbreviations. PaO_2: arterial oxygen tension; F_IO_2: inspiratory oxygen PSI: Pneumonia Severity Index; CURB-65 = confusion, blood-urea nitrogen, respiratory rate, blood pressure, age; ICU: intensive care unit. "Severe CAP": presence of at least one major criterion or three minor criteria according to the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines.

significantly shorter LOS as compared to non asthmatics (Table 5).

A multivariate analysis was performed to assess factors associated with prolonged length of hospital stay (LOS ≥6 days). Risk factors independently associated with prolonged LOS were: age≥65 yrs (odds ratio (OR) 2.6; 95% confidence interval (95%CI) 2.1—3.2; $p < 0.001$) previous alcohol abuse (OR 2.5; 95%CI 1.5—4.4; $p = 0.001$), cardiac failure (OR 1.6; 95%CI 1.2—2.1; $p = 0.001$) neurological disease (OR 1.4; 95%CI 1.1—1.8; $p = 0.012$), dyspnoea (OR 1.6; 95%CI 1.3—1.9; $p < 0.001$), C-RP ≥ 17 mg/dL (OR 1.4; 95%CI 1.1—1.7, $p = 0.002$), tachypnoea (respiratory rate ≥30 breaths/min) (OR 1.5; 95%CI 1.2—1.9; $p < 0.001$), altered mental status (OR 1.9; 95%CI 1.4—2.5; $p < 0.001$), pleural effusion (OR 2.6; 95%CI 1.9—3.5; $p < 0.001$), multilobar infiltration (OR: 1.8; 95%CI 1.4—2.3; $p < 0.001$), bacteraemia (OR 2.2; 95%CI 1.5—3.2; $p < 0.001$) and ICU admission (OR 9.6; 95%CI 6.3—14.8; $p < 0.001$). Asthma was not associated with prolonged LOS (univariate analysis, OR 0.7; 95%CI 0.5—1.0; $p = 0.085$) in the general population. The model to predict patients with prolonged length of hospital stay was well calibrated with *p*-value in Hosmer—Lemeshow test 0.50.

The multivariate analysis for prolonged LOS among asthmatic patients showed the following risk factors: age ≥ 65 yrs (OR 5.4; 95%CI 2.3—12.7; $p < 0.001$), multilobar infiltration (OR 5.3; 95%CI 1.6—17.0; $p = 0.005$) and ICU admission (OR 7.3; 95%CI 2.1—25.5; $p = 0.002$). The model to predict prolonged LOS among asthmatic patients was well calibrated with *p*-value in Hosmer—Lemeshow test 0.98.

Finally, the risk factors associated with 30-day mortality in the multivariate analysis were: age ≥ 65 yrs (OR 3.2; 95%CI

Table 3 Aetiological diagnosis of pneumonia in the 1704 patients with positive microbiology according to the presence of asthma.

Microorganism	Asthma-CAP *n*, (%) 139, (3.4%)	CAP *n*, (%) 3940, (96.6)	*P* value
Known aetiological diagnosis, *n* (%)	69 (50)	1635 (41)	0.06
Streptococcus pneumoniae, *n* (%)	33 (48)	687 (42)	0.34
Respiratory virus, *n* (%)	11 (16)	228 (14)	0.64
Mixed infections, [a]*n* (%)	9 (13)	213 (13)	>0.99
Atypical bacteria, *n* (%)	4 (6)	124 (7)	0.58
Mycoplasma pneumoniae, *n* (%)	3 (4)	59 (4)	0.75
Coxiella burnetii, *n* (%)	0 (0)	23 (1)	0.32
Chlamydia pneumoniae, *n* (%)	1 (1)	42 (3)	0.56
Legionella pneumophila, *n* (%)	2 (3)	117 (7)	0.17
***Enterobacteriaceae*, *n* (%)**			
Klebsiella spp., *n* (%)	1 (1)	6 (0.4)	0.17
Escherichia coli, *n* (%)	0 (0)	19 (1)	0.37
Proteus spp., *n* (%)	0 (0)	1 (0.1)	0.83
Non-fermentating gram-negative bacilli			
Pseudomonas aeruginosa, *n* (%)	1 (1)	42 (3)	0.56
Moraxella catarrhalis, *n* (%)	0 (0)	6 (0.4)	0.61
Haemophilus influenzae, *n* (%)	4 (6)	53 (3)	0.25
Staphylococcus aureus, *n* (%)	1 (4)	42 (3)	0.56
Streptococcus viridans, *n* (%)	0 (0)	11 (1)	0.49

Data about microorganisms are expressed as *n* and percentage of positive cultures.

[a] A mixed infection was described in 13% of both groups being the association of *S. pneumoniae* and respiratory virus the most frequent, particularly among asthmatics (asthma-CAP, $n = 6$ (9%) vs. CAP, $n = 54$ [3%]; $p = 0.017$) followed by *S. pneumoniae* plus *Haemophilus influenzae* (asthma-CAP, $n = 0$ [0%] vs. CAP, $n = 37$ [2%], $p = 0.21$), by *S. pneumoniae* plus *Pseudomonas aeruginosa* (asthma-CAP, $n = 0$ [0%] vs. CAP, $n = 10$ [1%], $p = 0.52$) and by *S. pneumoniae* plus *Chlamydia pneumoniae* (asthma-CAP, $n = 1$ [1%] vs. CAP, $n = 7$ [0.4%], $p = 0.22$). The other observed combinations were described in very low percentages each (<0.5%) in both groups.

1.9–5.4; $p < 0.001$), neurological disease (OR 2.4; 95%CI 1.7–3.5; $p < 0.001$), dyspnoea (OR 1.7; 95%CI 1.0–2.7; $p = 0.032$), creatinine≥1.5 mg/dL (OR 2.6; 95%CI 1.8–3.7; $p < 0.001$), tachypnoea (OR 2.1; 95%CI 1.5–3.0; $p < 0.001$) $PaO_2/F_IO_2 < 250$ (OR 2.9; 95%CI 2.0–4.1; $p < 0.001$), altered mental status (OR 2.6; 95%CI 1.8–3.8; $p < 0.001$), ICU admission (OR 2.0; 95%CI 1.3–3.0; $p = 0.001$). By contrast, prolonged LOS (≥6 days) was a protective factor for mortality (OR 0.5; 95%CI 0.3–0.7; $p < 0.001$) while there was no significant association with asthma. The Hosmer–Lemeshow goodness-of-fit test indicated that the model predictive of 30-day hospital mortality is well calibrated ($p = 0.19$).

In order to investigate the possible influence of ICs in asthmatic patients we analysed data of clinical presentation and main outcomes by comparing patients chronically receiving ICs with those not receiving them within the asthma-CAP group and found no significant differences (Table 6).

Discussion

The most important findings of our work are:

1. Only 3.4% of our CAP patients had asthma as comorbidity. These patients presented lower age, less smoking habit and similar data of clinical presentation in comparison with non-asthmatics, excepting hypoxaemia (less frequent) and lower severity indices (PSI, CURB-65, "severe CAP" cases.);

Table 4 Aetiology of bacteraemia.

Microorganism	Asthma-CAP *n*, 14	CAP *n*, 321	*P* value
Streptococcus pneumoniae	12 (86)	244 (76)	0.40
Staphylococcus aureus	1 (7)	15 (5)	0.67
Escherichia coli	1 (7)	12 (4)	0.52
Streptococcus viridans	0 (0)	12 (4)	>0.99
Haemophilus influenzae	0 (0)	8 (3)	>0.99
Enterococcus	0 (0)	4 (1)	>0.99
Klebsiella pneumoniae	0 (0)	4 (1)	>0.99
Proteus mirabilis	0 (0)	2 (0.6)	>0.99

Data are number of patients (%).
Abbreviations. CAP: community-acquired pneumonia.

Table 5 Pulmonary and extra-pulmonary complications, length of stay and outcomes of CAP according to presence and absence of asthma.

	Asthma-CAP *n*, (%) 139, (3.4%)	CAP *n*, (%) 3940, (96.6)	*P* value
Pulmonary complications, *n* (%)			
Empyema	2 (1)	49 (1)	0.85
Pleural effusion	22 (16)	529 (14)	0.47
Multilobar involvement	27 (21)	780 (22)	0.85
Acute respiratory distress	2 (2)	108 (3)	0.35
Systemic complications, *n* (%)			
Bacteraemia	14 (10)	321 (8)	0.42
Development of acute renal failure	16 (11)	887 (23)	**0.001**
Development of septic shock	4 (3)	209 (5)	0.21
Length of hospital stay, median (1st quartile; 3rd quartile)	6 (3; 9)	7 (4; 10)	**0.023**
ICU admission, *n* (%)	26 (19)	580 (15)	0.20
Non invasive mechanical ventilation, *n* (%)	3 (2)	137 (4)	0.40
Invasive mechanical ventilation, *n* (%)	3 (2)	155 (4)	0.29
30-day mortality, *n* (%)	6 (4)	285 (7)	0.19

Percentages calculated on non-missing data.
Abbreviations. SD: standard deviation; ICU: intensive care unit.

2. Clinical outcomes (mortality, MV) were similar for asthmatics and non asthmatic patients;
3. Previous ICs were not associated with better outcomes of CAP in asthmatic patients
4. Aetiological agents in asthma-CAP patients were similar to those of CAP group, being *S. pneumoniae* always the most frequently isolate.

To our knowledge this is the first study in the literature analysing a large CAP series investigating clinical features and microbial aetiology of pneumonia in asthma. To date, scarce information has been provided in the literature about the possible influence of asthma on clinical course of CAP. In 2010 Bewick et al. [23] described the prevalence of pneumococcal serotypes in a cohort of hospitalized CAP patients in UK and recorded an asthma prevalence of 11.1%.

Our results show only a low percentage of asthmatics that, in comparison with the general population, were younger and showed less smoking history. Different factors could justify this last difference in smoking prevalence, as the younger age of asthmatic patients or the impact of smoking on their respiratory symptoms. The younger age of asthmatic patients should also justify the lower rates of neurological comorbidities, of mental confusion at admission and of renal failure.

By contrast, we observed a higher rate of previous antibiotic treatment in the asthma-CAP group, a finding that could be justified by the recurrent exacerbations

Table 6 Complications and outcomes of Asthma-CAP according to ICs therapy.

	ICs therapy *n*, (%) 72 (51.8%)	Non ICs therapy *n*, (%) 67 (48.2%)	*P* value
Pulmonary complications, *n* (%)			
Empyema	0 (0)	2 (3)	0.13
Pleural effusion	10 (14)	12 (19)	0.47
Multilobar involvement	15 (23)	11 (18)	0.48
Acute respiratory distress	0 (0)	1 (2)	0.30
Severe CAP, *n* (%)	6 (9)	12 (20)	0.10
Systemic complications, *n* (%)			
Bacteraemia	5 (7)	8 (12)	0.29
Development of acute renal failure	8 (11)	7 (11)	0.93
Development of septic shock	2 (3)	2 (3)	>0.99
Length of hospital stay, median (1st quartile; 3rd quartile)	6 (4; 9)	5 (2; 8)	0.19
ICU admission, *n* (%)	10 (14)	15 (23)	0.16
Non-invasive mechanical ventilation, *n* (%)	2 (3)	1 (2)	>0.99
Invasive mechanical ventilation, *n* (%)	1 (2)	2 (3)	0.60
30-day mortality, *n* (%)	1 (1)	3 (5)	0.26

Percentages calculated on non-missing data.
Abbreviations. ICs: inhaled corticosteroids; CAP: community-acquired pneumonia; ICU: intensive care unit.

usually described in asthma. Nevertheless, it is general belief that viruses are the major causes for asthmatic exacerbations while bacterial infections are less relevant [12]. Apparently, our results may reveal a physician's tendency to prescribe frequently antibiotics for asthma exacerbations even without a microbiological support to cover eventual bacterial or mixed infection and to reduce the risk of severe asthma exacerbation. Nevertheless a panel of experts do not recommended antibiotic use for asthma exacerbations in [24] (www.ginasthma.org, update 2012).

Asthmatic patients showed an influenza vaccination rate similar to the non-asthmatics despite their younger age, suggesting that the general recommendation to vaccinate moderate-to-severe asthma patients is possibly applied [1]. On the other side, there was a trend to a lower pneumococcal vaccination rate. Indeed, current international recommendations do not suggest pneumococcal vaccination for asthmatics (www.ginasthma.org update 2012) possibly due to contrasting data [13,14,18]. On the other side CDC recommends pneumococcal vaccination in asthma since 2010 [25]. In our study it is worth remarking the very low prevalence of asthma among CAP patients (3.4%) and that the pneumococcal bacteraemia rates were similar comparing asthma to non-asthma patients (86% vs. 76%, Table 4). Conversely, a higher risk of IPD in asthma patients has been described previously [13,14].

The asthmatic patients of our series presented with more dyspnoea and pleuritic pain but showed, overall, less severe pneumonia (PSI, hypoxaemia, etc). The clinical outcomes of asthmatic patients were in general similar to those of the CAP group. In fact, asthmatics showed a significantly shorter (2 days) LOS but equal rates of MV and mortality (the limited sample size being potentially responsible for the lack of statistically significance). As a confirmation, both multivariate analyses for 30-day mortality and prolonged LOS did not show any association (positive or negative) with asthma. Likely, the potential excess pneumonia severity that could be expected in relation to asthma is counterbalanced by younger age and less co-morbidities of these patients, resulting finally in similar outcomes. In addition, the characteristic airways inflammation of asthma, potentially detrimental in CAP, does not seem to negatively influence CAP outcomes. Indeed, we could conclude that CAP does not need a special attention in the asthmatic population, although an exception could be eventually considered for very severe asthma where airways remodelling and advanced lung damage could complicate pneumonia evolution.

Microbiological investigation in our patients showed that pneumonia in asthma is usually caused by usual CAP pathogens (*S. pneumoniae*, etc.). Therefore, our microbiological findings on aetiology of CAP cannot sustain the general concept of an increased prevalence of viral infections (although the combination of *S. pneumoniae* and viruses was more frequent in asthma patients groups). The clear microbiological similarities observed between asthma-CAP and general CAP groups also indicate that empiric treatment of CAP in asthmatics should follow current guidelines for CAP.

As expected, asthmatics showed a higher rate of previous ICs therapy being these drugs fundamental to control asthma. While the risky association between ICs and CAP has been well demonstrated in COPD [26—28], these data are not confirmed in asthma [29—31]. Some observational studies have showed that ICs therapy is not a risk factor for CAP in asthma [29,30]. On the other hand we cannot demonstrate a protective effect of ICs in pneumonia complications or outcomes as it has been demonstrated in COPD patients chronically treated with these drugs [32—34]. These differences have to be explained by substantial differences in the host settings and in the innate immunity between asthma [8] and COPD patients. Our results show that apparently chronic ICs do not have any influence on major CAP outcomes in asthma and this is fully consistent with the prospective study from Yamada et al. supporting the idea that CAP patho-physiology in asthma is different than in COPD [35].

The major strength of this work is that, to our knowledge, it is the first large CAP series analysing demographics, clinical characteristics, microbial aetiology and outcomes of pneumonia in asthmatic patients.

The possible limitation is that this study was performed in a single European country (2 centres from Spain) and could not reflect epidemiology of CAP in asthmatics elsewhere. Moreover, due to the nature of our data (database mainly focused on CAP description and not at asthma follow-up) it is likely we are underestimating the asthma prevalence in our population since spirometry was not available for all our patients and we had to use a multifactorial definition of asthma and a second cases' check by a pulmonologist expert in asthma in order to exclude all potential mistakes (COPD etc) and to improve the quality of our data.

Conclusions

Our study shows low asthma prevalence in a large CAP population and that clinical outcomes of CAP in asthmatics are similar to the general population. Furthermore, microbial aetiology of asthma-CAP did not differ from the general population. Our data suggest that management of CAP in asthma should not differ from the general population and current antibiotic recommendations [19] should be considered fully valid for this subset of the population.

Author contributions

All the authors have contributed to the manuscript and approved its last version.

Dr. Silvia Terraneo and Dr. Eva Polverino are the main investigators of the study, directly involved in the project design, data collection and analysis, and the main authors of the manuscript.

Dr. Catia Cilloniz, Dr. Rosanel Amaro, Dr. Beatriz Montull were directly involved in patients' recruitment and data collection and reviewed and approved the final version of the manuscript.

Dr. Mª Carmen Vennera is the asthma consultant who supervised the asthma patients' recruitment by reviewing clinical history and data collection; contributed to and approved the final manuscript.

Albert Gabarrus is the biomedical statistician who performed the statistical analysis of the manuscript.

Encarnacion Moreno is the research nurse involved in data collection and samples management.

Dr. Rosario Menendez and Dr. Stefano Centanni contributed to the design of the project, and contributed to and approved the final manuscript.

Prof. Antoni Torres led the study group, contributed to the design of the project, and contributed to and approved the final study; he is the guarantor of the entire manuscript.

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Conflict of interests statement

The authors declare that have no conflicts of interest to declare regarding this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.09.001.

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